Amendments to the Specification:

On page 1, line 16, please replace the paragraph beginning with the phrase "A variety of approaches have been taken to identify genes" with the following amended paragraph:

A variety of approaches have been taken to identify genes and pathways that are associated with traits, such as human disease. In one approach, attempts have been made to use gene expression data to identify genes and pathways associated with such traits. In another approach, genetic information has been used to attempt to identify genes and pathways associated with traits. For instance, clinical measures of a population **[[cab]]** can be taken to study a trait such as a disease found in the population. Risk factors for the trait can be established from these clinical measures. Demographic and environmental factors are further used to explain variation with respect to the trait. Further, genetic variations associated with traits, such as disease-related traits, as well as the disease itself are used to identify regions in the genome linked to a disease. For example, genetic variations in a population may be used to determine what percentage of the variation of the trait in the population of interest can be explained by genetic variation of a single nucleotide polymorphism (SNP), haplotype, or short tandem repeat (STR) marker. However, as will be described below, the elucidation of genes involved in biological pathways that influence a trait, such as a disease, using either gene expression or genetic expression approaches, is problematic and generally not successful in many instances.

On page 29, line 28, please replace the paragraph beginning with the phrase "Other suitable sources of genetic markers" with the following amended paragraph:

Other suitable sources of genetic markers include databases that have various types of gene expression data from platform types such as spotted microarray (microarray), high-density oligonucleotide array (HDA), hybridization filter (filter) and serial analysis of gene expression (SAGE) data. Another example of a genetic database that can be used is a DNA methylation database. For details on a representative DNA methylation database, see Grunau *et al.*, 2001 ~~in press~~, MethDB- a public database for DNA methylation data, ~~*Nucleic Acids Research*~~ Nucleic Acids Research 29, 270-274; or the URL: ~~http://~~genome.imb-jena.de/public.html.

On page 30, line 3, please replace the paragraph beginning with the phrase "In one embodiment of the present invention, a set of markers" with the following amended paragraph:

In one embodiment of the present invention, a set of markers is derived from any type of genetic database that tracks variations in the genome of an organism of interest. Information that is typically represented in such databases is a collection of locus within the genome of the organism of interest. For each locus, strains for which genetic variation information is available are represented. For each represented strain, variation information is provided. Variation information is any type of genetic variation information. Representative genetic variation information includes, but is not limited to, single nucleotide polymorphisms, restriction fragment length polymorphisms, microsatellite markers, restriction fragment length polymorphisms, and short tandem repeats. Therefore, suitable genotypic databases include, but are not limited to:

Genetic variation type	Uniform resource location
SNP	~~http://~~bioinfo.pal.roche.com/usuka_bioinformatics/cgi-bin/msnp/msnp.pl
SNP	~~http://~~snp.cshl.org/
SNP	~~http://www.~~ibc.wustl.edu/SNP/
SNP	~~http://~~www-genome.wi.mit.edu/SNP/mouse/
SNP	~~http://www.~~ncbi.nlm.nih.gov/SNP/
Microsatellite markers	~~http://www.~~informatics.jax.org/searches/polymorphism_form.shtml
Restriction fragment length polymorphisms	~~http://www.~~informatics.jax.org/searches/polymorphism_form.shtml
Short tandem repeats	~~http://www.~~cidr.jhmi.edu/mouse/mmset.html
Sequence length polymorphisms	~~http://~~mcbio.med.buffalo.edu/mit.html
DNA methylation database	~~http://~~genome.imb-jena.de/public.html
Short tandem-repeat polymorphisms	Broman *et al.*, 1998, Comprehensive human genetic maps: Individual and sex-specific variation in recombination, American Journal of Human Genetics 63, 861-869
Microsatellite markers	Kong *et al.*, 2002, A high-resolution recombination

Genetic variation type	Uniform resource location
	map of the human genome, Nature Genetics ~~Nat Genet~~ 31, 241-247

On page 30, line 15, please replace the paragraph beginning with the phrase "In addition, the genetic variations used by" with the following amended paragraph:

In addition, the genetic variations used by the methods of the present invention can involve differences in the expression levels of genes rather than actual identified variations in the composition of the genome of the organism of interest. Therefore, genotypic databases within the scope of the present invention include a wide array of expression profile databases such as the one found at the URL: ~~http://www.~~ncbi.nlm.nih.gov/geo/.

On page 71, line 27, please replace the paragraph beginning with the phrase "Many known programs can be used to perform linkage analysis" with the following amended paragraph:

Many known programs can be used to perform linkage analysis in accordance with this aspect of the invention. One such program is MapMaker/QTL, which is the companion program to MapMaker and is the original QTL mapping software. MapMaker/QTL analyzes F_2 or backcross data using standard interval mapping. Another such program is QTL Cartographer, which performs single-marker regression, interval mapping (Lander and Botstein, ~~*Id.*~~ 1989, "Mapping Mendelian factors underlying quantitative traits using RFLP linkage maps," Genetics 121: 185-199), multiple interval mapping and composite interval mapping (Zeng, 1993, ~~PNAS~~ Proceedings of the National Academy of Sciences USA 90: 10972-10976; and Zeng, 1994, Genetics 136: 1457-1468). QTL Cartographer permits analysis from F_2 or backcross populations. QTL Cartographer is available from ~~http://~~statgen.ncsu.edu/qtlcart/cartographer.html (North Carolina State University). Another program that can be used by processing step ~~114~~ 210 is Qgene, which performs QTL mapping by either single-marker regression or interval regression (Martinez and Curnow, 1994, Heredity 73:198-206). Using Qgene, eleven different population types (all derived from inbreeding) can be analyzed. Qgene is available from ~~http://www.~~qgene.org[[/]]. Yet

another program is MapQTL, which conducts standard interval mapping (Lander and Botstein, ~~, *Id.*~~ 1989, "Mapping Mendelian factors underlying quantitative traits using RFLP linkage maps," Genetics 121: 185-199), multiple QTL mapping (MQM) (Jansen, 1993, Genetics 135: 205-211; Jansen, 1994, Genetics 138: 871-881), and nonparametric mapping (Kruskal-Wallis rank sum test). MapQTL can analyze a variety of pedigree types including outbred pedigrees (cross pollinators). MapQTL is available from Plant Research International, Plant Research International, P.O. Box 16, 6700 AA Wageningen, The Netherlands; ~~http://www.~~plant.wageningen-ur.nl/default.asp?section=products[[)]]. Yet another program that may be used in some embodiments of processing step 210 is Map Manager QT, which is a QTL mapping program (Manly and Olson, 1999, ~~Mamm~~ Mammalian Genome 10: 327-334). Map Manager QT conducts single-marker regression analysis, regression-based simple interval mapping (Haley and Knott, 1992, Heredity 69, 315-324), composite interval mapping (Zeng 1993, Proceedings of the National Academy of Sciences USA ~~PNAS~~ 90: 10972-10976), and permutation tests. A description of Map Manager QT is provided by the reference Manly and Olson, 1999, Overview of QTL mapping software and introduction to Map Manager QT, Mammalian Genome 10: 327-334.

On page 72, line 30, please replace the paragraph beginning with the phrase "Still another program that can be used to perform linkage analysis" with the following amended paragraph:

Still another program that can be used to perform linkage analysis is QTL Café. The program can analyze most populations derived from pure line crosses such as F_2 crosses, backcrosses, recombinant inbred lines, and doubled haploid lines. QTL Café incorporates a Java implementation of Haley & Knotts' flanking marker regression as well as Marker regression, and can handle multiple QTLs. The program allows three types of QTL analysis single marker ANOVA, marker regression (Kearsey and Hyne, 1994, Theoretical Applied Genetics ~~Theor. Appl. Genet.~~, 89: 698-702), and interval mapping by regression, (Haley and Knott, 1992, Heredity 69: 315-324). ~~QTL Café is available from http://web.bham.ac.uk/g.g.seaton/.~~

On page 73, line 5, please replace the paragraph beginning with the phrase "Yet another program that can be used to perform linkage analysis" with the following amended paragraph:

Yet another program that can be used to perform linkage analysis is MAPL, which performs QTL analysis by either interval mapping (Hayashi and Ukai, 1994, ~~Theor. Appl. Genet.~~ Theoretical Applied Genetics 87:1021-1027) or analysis of variance. Different population types including F_2, back-cross, recombinant inbreds derived from F_2 or back-cross after a given generations of selfing can be analyzed. Automatic grouping and ordering of numerous markers by metric multidimensional scaling is possible. ~~MAPL is available from the Institute of Statistical Genetics on Internet (ISGI), Yasuo, UKAI, http://web.bham.ac.uk/g.g.seaton/.~~

On page 73, line 12, please replace the paragraph beginning with the phrase "Another program that can be used for linkage analysis is" with the following amended paragraph:

Another program that can be used for linkage analysis is R/qtl. This program provides an interactive environment for mapping QTLs in experimental crosses. R/qtl makes ~~uses~~ use of the hidden Markov model (HMM) technology for dealing with missing genotype data. R/qtl has implemented many HMM algorithms, with allowance for the presence of genotyping errors, for backcrosses, intercrosses, and phase-known four-way crosses. R/qtl includes facilities for estimating genetic maps, identifying genotyping errors, and performing single-QTL genome scans and two-QTL, two-dimensional genome scans, by interval mapping with Haley-Knott regression, and multiple imputation. R/qtl is available from Karl W. Broman, Johns Hopkins University, ~~http://~~biosun01.biostat.jhsph.edu/~kbroman/qtl/.

On page 74, line 16, please replace the paragraph beginning with the phrase "In some embodiments of the present invention, linkage analysis is performed" with the following amended paragraph:

In some embodiments of the present invention, linkage analysis is performed using the algorithm of Lander, as implemented in programs such as GeneHunter. See, for example, Kruglyak *et al.*, 1996, Parametric and Nonparametric Linkage Analysis: A Unified Multipoint Approach, American Journal of Human Genetics 58:1347-1363[[,]]; Kruglyak and Lander, 1998, Journal of Computational Biology 5:1-7; and Kruglyak, 1996, American Journal of Human Genetics 58, 1347-1363. In such embodiments, unlimited markers may be used but pedigree size is constrained due to computational limitations. In other embodiments, the MENDEL software package is used. (See ~~http://~~bimas.dcrt.nih.gov/linkage/ltools.html). In such embodiments, the size of the pedigree can be unlimited but the number of markers that can be used in constrained due to computation limitations. The techniques described in this Section typically require an inbred population.

On page 93, line 10, please replace the paragraph beginning with the phrase "In some embodiments of step 1914" with the following amended paragraph:

In some embodiments of step 1914, an eQTL/cQTL are not considered to be colocalized, no matter how close the eQTL and cQTL are unless the QTL (the position of the eQTL/cQTL overlap) is truly common to the clinical and expression trait (pleiotropic effect) rather than simply representing two closely linked QTL (linkage disequilibrium). Thus, in some embodiments of step 1914, in order to achieve the result 1914-Yes, the subject eQTL and cQTL must pass a pleiotropy test. In one embodiment of the present invention, the ~~test~~ pleiotropy test operates by testing the positions between the eQTL and the cQTL to determine whether the positions are statistically indistinguishable.

On page 98, line 12, please replace the paragraph beginning with the phrase "Figure 25 provides a hypothetical example of a validation strategy" with the following amended paragraph:

Figure 25 provides a hypothetical example of a validation strategy in accordance with one embodiment of the present invention. In this example, genes Y1 through Y4 are genes

that are part of an expression pattern associated with a complex trait of interest. The upper panel plots the lod score curves for the four genes for a particular chromosome, where the cluster of eQTL depicted are coincident with a cQTL for the complex trait. By examining genes that physically reside in the QTL support interval, those genes that have cis-acting eQTL that are significantly genetically interacting with the other eQTL/cQTL are identified. These genes represent the potential causative genes underlying the cQTL/eQTL. Gene X in Fig. 25 highlights one such example. By knocking gene X out using in vivo small interfering RNA (siRNA) methods, the siRNA knock-out animals can be profiled and the genetic signatures of the original genes making up the eQTL cluster examined. Various siRNA knock-out techniques (also referred to as RNA interference or post-transcriptional gene silencing) are disclosed, for example, in Xia, *et al.*, 2002, Nature Biotechnology 20, p. 1006; Hannon, 2002, Nature 418, p. 244; Carthew, 2001, Current Opinion in Cell Biology 13, p. 244; Paddison, 2002, Genes & Development 16, p. 948; Paddison & Hannon, 2002, Cancer Cell 2, p. 17; Jang *et al.*, 2002, Proceedings of the National Academy of ~~Science~~ Sciences USA 99, p. 1984; Martinez *et al.*, 2002, Proceedings of the National Academy of ~~Science~~ Sciences USA 99, p. 14849.